

## EDITORIAL COMMENT

# How Does Elevated Lipoprotein(a) Cause Aortic Valve Stenosis?\*



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Lipoprotein(a) [Lp(a)] was discovered in 1963 by Kaare Berg in Norway, and elevated levels were already then considered a cardiovascular risk factor (1). For many years, Lp(a) received only moderate scientific and clinical attention; however, in recent years, important new evidence has emerged, and elevated Lp(a) is now considered a causal risk factor for cardiovascular disease. Genetic variants in the *LPA* gene, which is responsible for encoding apolipoprotein(a) [apo(a)] and determining elevated Lp(a) levels, are associated with coronary heart disease (2,3).

Other exciting new discoveries include evidence that elevated Lp(a) levels likewise are a causal risk factor for aortic valve calcification and stenosis (4,5). In aortic valve stenosis, thickening of the aortic valve cusps limits the outflow of blood from the left ventricle of the heart, a condition that, if untreated, can lead to heart failure and premature death. Aortic valve stenosis affects ~2% of individuals ≥65 years of age, and in those who have symptoms, 5- and 10-year mortality approaches 50% and 90%, respectively, without aortic valve replacement (AVR) (6). Randomized trials using statins and other lipid-lowering medications have failed to show an effect on aortic valve stenosis, and to date, the only effective treatment is AVR. Previously, risk factors for aortic valve

stenosis included only bicuspid aortic valves and rheumatic fever. Recently, however, common cardiovascular risk factors such as smoking, high blood pressure, high cholesterol, diabetes, male sex (6), and now elevated Lp(a) (4,5) have emerged. As for aortic valve stenosis, Lp(a) is also a causal risk factor for atherosclerotic stenosis (7).

How elevated Lp(a) levels lead to aortic valve and atherosclerotic stenosis is not completely clear, but there are several proposed mechanisms (8,9). First, as Lp(a) consists of a low-density lipoprotein (LDL) cholesterol-rich particle covalently bound to an apo(a) glycoprotein, 1 possible mechanism suggests that Lp(a), after transfer from the bloodstream into the wall of aortic valve cusps and the arterial intima, leads to cholesterol deposition in a manner similar to LDL cholesterol. This would then cause a thickening of aortic valve cusps and the arterial intima. Second, as apo(a) resembles plasminogen (8,9), Lp(a) may promote thrombosis by competing with plasminogen and thereby inhibiting the role of plasmin in dissolving fibrin clots (10). This could then, through fibrin deposition, lead to progressive aortic valve and atherosclerotic stenosis. Third, Lp(a) may be important in wound healing (11): it is possible that Lp(a) could bind to fibrin and be transported to and accumulate at sites of injury, thereby delivering cholesterol via its LDL component to sites of tissue healing and thus becoming part of the wound-healing process. If Lp(a) accumulates at sites of wound healing, then it can be speculated that Lp(a) might also accumulate at sites of minor injury at the very beginning of aortic valve and atherosclerotic stenosis, enhancing the deposition of cholesterol (11,12) and, possibly, thrombi. Either of these may lead to further stenosis. Indeed, Lp(a), as opposed to LDL, preferentially accumulates at sites of arterial injury (13), which seems to support the speculation that Lp(a) may contribute to wound healing in a normal

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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physiological way, whereas very high Lp(a) levels could pathologically lead to aortic valve stenosis (4,5) and atherosclerotic stenosis (7). That said, the precise molecular mechanism by which elevated levels of Lp(a) may promote cholesterol deposition, thrombosis, and/or wound healing, eventually causing aortic valve and atherosclerotic stenosis, is not well understood.

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In this issue of the *Journal*, Capoulade et al. (14) report on 220 patients with mild-to-moderate aortic valve stenosis who were followed for 3.5 years, observing that both elevated levels of Lp(a) and elevated levels of oxidized phospholipids on apolipoprotein B are associated with increased progression of aortic valve stenosis. These are novel, timely, and important findings. As oxidized phospholipids are carried mainly by Lp(a) (15), it is speculated that Lp(a) as an independent predictor of aortic valve stenosis could be explained by oxidized phospholipids (14). Wisely, as levels of Lp(a) and oxidized phospholipids are highly correlated, and as the results for the 2 measurements are almost identical, Capoulade et al. (14) never conclude that oxidized phospholipids are the cause of aortic valve stenosis progression. Interestingly, the relative progression rate of aortic valve stenosis for high versus low Lp(a) levels was most pronounced in individuals  $\leq 57$  years of age, suggesting that because of the strong genetic determination of Lp(a), its pathological role is most pronounced in the young (14).

Capoulade et al. (14) also speculate mechanistically on how oxidized phospholipids can lead to aortic valve stenosis through pro-inflammatory and pro-calcifying effects, but no data are presented to support such hypotheses. Interestingly, in a study of >100,000 individuals, we recently observed no causal association between elevated levels of Lp(a) and

whole body low-grade inflammation as determined by measurements of C-reactive protein, despite a causal association with aortic valve stenosis and myocardial infarction (16). Our study cannot exclude inflammation locally at aortic valve cusps or in the arterial intima. However, we believe that it is prudent to also consider the possibility that elevated Lp(a) could lead to aortic valve and atherosclerotic stenosis by mechanisms independent of inflammation and oxidized phospholipids on Lp(a), such as through the kringle IV, type 2 size polymorphism in apo(a), the main genetic determinant of Lp(a) levels. Also, it should be considered that the measurement of oxidized phospholipids might act as an indirect measurement of Lp(a) levels and thus of the kringle IV, type 2 size polymorphism.

Future research should: 1) provide a better understanding of how elevated Lp(a) causes aortic valve and atherosclerotic stenosis, including the potential role of oxidized phospholipids; 2) confirm the findings of Capoulade et al. (14) in larger and better-powered studies; 3) address whether oxidized phospholipids provide important evidence beyond the mere measurement of Lp(a) levels; and finally and of utmost importance, 4) include randomized trials aimed at reducing Lp(a) and oxidized phospholipids to hopefully reduce the risk of aortic valve and atherosclerotic stenosis and, as a consequence, reduce the risk of AVR surgery and coronary heart disease. Such additional evidence will help us better understand the precise molecular mechanism of how elevated Lp(a) causes aortic valve and atherosclerotic stenosis.

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**KEY WORDS** aortic valve replacement, apolipoprotein(a), oxidized phospholipids, wound healing